ACTIVIN TYPE 2 RECEPTOR BINDING PROTEINS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of U.S. application Ser. No. 16/390,394, filed Apr. 22, 2019, which is a divisional of U.S. application Ser. No. 15/456,392, filed Mar. 10, 2017, which claims the benefit of U.S. Provisional Appl. No. 62/306,354, filed Mar. 10, 2016, each of which is incorporated herein by reference.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The content of the electronically submitted sequence listing in ASCII text file APH-00402 SL.txt (Size: 182,831 bytes; and Date of Creation: Aug. 16, 2019) filed with the application is herein incorporated by reference in its entirety.

BACKGROUND

[0003] The transforming growth factor-beta (TGF-beta) family contains a variety of growth factors that are known to exert biological effects on a large variety of cell types in both vertebrates and invertebrates. Members of the TGF-beta family perform important functions during embryonic development in pattern formation and tissue specification and can influence a variety of differentiation processes, including adipogenesis, myogenesis, chondrogenesis, cardiogenesis, hematopoiesis, neurogenesis, and epithelial cell differentiation. The family includes proteins that are variously described as Growth and Differentiation Factors (GDFs), Bone Morphogenetic Proteins (BMPs), activins and inhibins.

[0004] TGF-beta family members transduce signals through a mechanism that includes a multistep process in which the TGF-beta family member binds a type II serine/threonine kinase receptor expressed on the cell surface, the type II receptor forms a heteromeric complex with a cognate type I receptor and activates the type I receptor through phosphorylation, the activated type-I receptor phosphorylates and activates Smad proteins that transduce the signal from the cytoplasm to the nucleus, and nuclear Smad oligomers bind to DNA and associate with transcription factors to regulate the expression of target genes.

[0005] Two related type II TGF-beta receptor family members, ActRIIB and ActRIIA, have been identified as type II receptors for activin A and activin B and other TGF-beta family members including BMP7, BMP9, BMP10, GDF1, GDF3, GDF8 (myostatin), GDF11, and Nodal (Yamashita et al., *J. Cell Biol.* 130:217-226 (1995); Lee et al., *PNAS* 98:9306-9311 (2001); Yeo et al., *Mol. Cell* 7:949-957 (2001); and Oh et al., *Genes Dev.* 16:2749-54 (2002)). ALK4 and ALK7 are the primary type I TGF-beta receptor family member receptors for activin A and activin B, respectively.

[0006] Alterations in the expression and activity of members of the TGF-beta ligand and receptor families have been proposed to be associated with a variety of disorder and conditions including muscle, bone, neurological and metabolic disorders and conditions, and cancer. It is an object of this disclosure to provide ActRII antagonists and uses for the same in the diagnosis and treatment, prevention and/or amelioration of a disease or condition associated with ActRII and/or ActRII ligands.

BRIEF SUMMARY

[0007] The disclosure provides activin receptor type II (ActRII)-binding proteins and methods of using the ActRII-binding proteins. In particular aspects, the ActRII-binding proteins are capable of inhibiting or blocking the binding of ActRII to one or more cognate ActRII ligands and/or one or more cognate ActRI receptors. In some aspects, the ActRII-binding proteins are capable of inhibiting or blocking the binding to ActRII to an ActRII ligand (e.g., activin A, activin B, GDF1, GDF3, GDF8 (myostatin), GDF11, BMP6, BMP7, BMP9, or BMP10). The disclosure also provides methods of using ActRII-binding proteins for the diagnosis, or treatment, prevention and/or amelioration of a disease or condition associated with ActRII expression and/or elevated ActRII-mediated signaling. Such diseases or conditions include, but are not limited to, muscle disorders such as degenerative muscle disease, muscular dystrophy, muscle atrophy, or muscle wasting disorders; a fibrotic condition; an inflammatory, autoimmune, cardiovascular, pulmonary, musculoskeletal, skeletal, ocular, neurologic, or metabolic disease or condition; obesity; wound healing; and cancer.

[0008] In some aspects, the ActRII-binding protein specifically binds ActRIIB. In further aspects, the provided ActRII-binding protein specifically binds ActRIIB and has at least one characteristic selected from the group consisting of: (a) competes with an ActRII ligand (e.g., activin A, activin B, GDF1, GDF3, GDF8 (myostatin), GDF11, BMP6, BMP7, BMP9, or BMP10) for binding to ActRIIB; (b) decreases the phosphorylation of ALK4 and/or ALK7 in cells expressing ActRIIB and ALK4 and/or ALK7 in the presence of an ActRIIB ligand (e.g., activin A and/or GDF8 (myostatin)); (c) decreases the phosphorylation of Smads (e.g., Smad2 and/or Smad3) in cells expressing ActRIIB in the presence of an ActRIIB ligand (e.g., activin A and/or GDF8); and (d) binds to ActRIIB with a K_D of ≤1 nM and ≥1 pM (e.g., as determined by BIACORE® analysis). In some aspects, the ActRIIB-binding protein has 2, 3, or 4 of the above characteristics. In some aspects, the ActRIIB-binding protein has at least 2 or at least 3 of the above characteristics. In further aspects, the ActRIIB-binding protein competes for binding to ActRIIB with an antibody having an ActRIIB-binding VH and VL pair disclosed herein. In further aspects, the ActRIIB-binding protein is an anti-ActRIIB antibody or an ActRIIB-binding antibody fragment.

[0009] In some aspects, the ActRII-binding protein specifically binds ActRIIB and ActRIIA. In further aspects, the provided ActRII-binding protein specifically binds ActRIIB and ActRIIA and has at least one characteristic selected from the group consisting of: (a) competes with an ActRII ligand (e.g., activin A, activin B, GDF1, GDF3, GDF8 (myostatin), GDF11, BMP6, BMP7, BMP9, or BMP10) for binding to ActRIIB and/or ActRIIA; (b) decreases the phosphorylation of ALK4 and/or ALK7 in cells expressing ActRIIB and/or ActRIIA, and ALK4 and/or ALK7, in the presence of an ActRIIB and/or ActRIIA ligand (e.g., activin A and/or GDF8 (myostatin)); (c) decreases the phosphorylation of Smads (e.g., Smad2 and/or Smad3) in cells expressing ActRIIB and/or ActRIIA in the presence of an ActRIIB and/or ActRIIA ligand (e.g., activin A and/or GDF8); and (d) binds to ActRIIB with a K_D of ≤1 nM and ≥1 pM (e.g., as